REMARKS

Claims 69-80, 83-94, 124-127, 129, 130 and 132-189 are pending. Claims 123, 128 and 131 have been canceled. Claims 69, 90, 124-127, 129, 130, 133, 135-140, 153, 156-159 and 160 have been amended. New claims 164-189 have been added. Support for the new claims can be found throughout the present application. No new matter has been added.

Election/Restrictions

The Examiner has indicated that claims 160-163 are drawn to "an invention that is independent or distinct from the invention originally claimed" (Office Action, pp. 2-3). The Examiner stated that these claims "are materially distinct, and differ at least in objectives, method steps, reagents, and/or dosages and/or schedules used, response variables, and criteria for success." (Office Action, p. 2) Applicants respectfully submit that the restriction requirement is improper and should be withdrawn.

35 U.S.C. §121 allows for the issuance of a restriction requirement when two or more independent or distinct inventions are claimed in the same application. This is not the case in the present application. Dependent claim 160, as amended, is drawn to methods according to claims 69, 83, 89, or 126, wherein the antibody or antigen-binding portion thereof is administered in conjunction with a second therapeutic modality. Claims 161-163 depend either directly or indirectly from claim 160. By definition, these claims are not "independent," as the restricted claims include the steps recited in the claims from which it depends (MPEP §802.01, "the term independent (*not dependent*) means there is no disclosed relationship between the two or more subjects disclosed." (emphasis added)). There is most certainly a disclosed relationship between these groups of claims–they are all drawn to the administration of anti-PSMA antibodies. In addition, they are not sufficiently distinct to merit restriction. The methods of claim 160-163 cannot be practiced without also practicing the methods of the claims from which they depend. The fact that claims 160-163 recite an additional step in the method does not render them distinct or independent. Furthermore, the objectives of claims 160-163 would be the same as the rest of the claims in the present application, namely, treating, preventing, or delaying development or

progression of prostate cancer. The fact that dosages, schedules, or reagents may differ is irrelevant, as such limitations are not recited in the claim. Finally, there is no serious burden imposed on the Examiner to support the restriction requirement, in part because, in this case, a finding that the base claims are patentable over the art necessarily means that the dependent claims are patentable over the art. For these reasons, the restriction requirement is improper, and Applicants respectfully request that it be withdrawn.

Claim Objections

Claim 139 was objected to by the Examiner for reciting "further comprises a cytotoxic drug" with regards to claim 127. Claim 139 has been amended to delete the reference to claim 127. Therefore, Applicants request withdrawal of the objection.

Claim Rejections -- 35 U.S.C. §112, 1st paragraph

The Examiner has rejected claims 69-80, 83-94, 123-136, and 123-159 under 35 U.S.C. §112, 1st paragraph for scope of enablement. Applicants thank the Examiner for acknowledging that the treatment of prostate cancer using the methods of the invention is enabled, and traverse the Examiner's assertion that preventing or delaying development or progression of prostate cancer is not enabled.

The Examiner states that "the essential validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of a clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent." (Office Action, p. 4)

To receive regulatory approval of a preventive therapeutic, such data may be necessary. However, patentability does not require such proof. A patent application is not an application for FDA approval, and human experimentation and data are not required for patentability. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) which held that human experimentation is not required, is apposite. *In re Brana* dealt with claims to chemical compounds for use as antitumor substances. The specification included evidence of antitumor activity in an animal model. The court held

that the showing of activity in an animal model was sufficient for patentability, and that human experimentation was not necessary.

The Applicants have provided much more than animal data. It has been demonstrated that the antibodies of the invention can bind to and ablate PSMA expressing cells, *in vivo*, in human beings. Furthermore, the Applicants have demonstrated that PSMA is differentially expressed during the progression of prostate cancer from normal cells, to benign hyperplastic cells, to cancerous cells. Applicants have also shown that the antibodies bind to benign hyperplastic prostate cells, which are pre-cancerous. Since benign prostatic hyperplasia can progress to prostate cancer, it is clear from the evidence presented by the Applicants that treatment with the antibodies using the methods of the invention would lead to the ablation of benign hyperplastic prostate cells thereby preventing or delaying the development or progression of prostate cancer.

The fact is that clinical testing must begin with the sickest patients with the most advanced cancers, and only much later can approval be obtained for experiments involving healthier patients. The holding of *In re Brana* teaches that, while it is good and necessary for the FDA to protect the public health by requiring evidence of safety and efficacy in humans, it is neither necessary nor desirable for the USPTO to have the same standards. What might be required to get approval from the FDA for testing in earlier-stage patients has no relevance for the issue of usefulness and patentability. As one example, the Her-2 antibody, which has been approved by the FDA for a number of years for the treatment of breast cancer, is only now being explored clinically for earlier stages of the disease. See Bange et al., Nature Medicine 7(5):548-552 (2001).

Identifying individuals who would benefit from administration of the antibodies to prevent or delay progression or development of prostate cancer is straightforward. As previously noted, diagnostic tests are known that can indicate the existence of a pre-cancerous or early cancerous condition such as benign prostatic hyperplasia. Once the presence of the pre- or early-cancerous condition is established, the administration of the antibodies would be useful to ablate the PSMA-expressing cells associated with that condition, thereby delaying or preventing the progression or development of prostate cancer.

In addition, evidence currently of record indicates that treatment of humans with the claimed anti-PSMA antibodies can delay or prevent progression of advanced prostate cancer. For example, treatment of patients with late-onset prostate cancer with the J591 antibody delayed progression of the disease by delaying death and increasing longevity, see, e.g., Exhibits M-O attached to the Response filed October 28, 2002. Applicants also have data demonstrating that treatment of mouse models of prostate cancer with the J591 antibody delays progression of disease by inhibiting androgen-independent prostate tumor growth. Thus, Applicants have clearly provided sufficient guidance and evidence to demonstrate that the claimed antibodies can be used to prevent or delay progression or development of prostate cancer. The Examiner's insistence on human data to correlate a preventative effect of the claimed antibodies is unfounded and contrary to the law.

Claims 123, 128-131, and 137-159 were rejected as "containing subject matter which was not described in the specification in such as way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Office Action, p. 6) In particular, the Examiner asserts that "there is no support in the specification for the specific type of antibody referred to as IgG." (Office Action, p. 6) While Applicants do not agree with the Examiner's assertions, in order to expedite prosecution, claims reciting the IgG limitation have been cancelled.

The Examiner further states that the specification does not provide written description for antibodies other than E99, J415, J533 or J591. Specifically, the Examiner asserts that "the results do not provide evidence of or a written description for other antibodies (or antigen binding portions thereof) which compete for binding to PSMA with a monoclonal antibody selected from the group consisting of E99, J415, J533 or J591." (Office Action, p. 7) Applicants respectfully traverse this rejection. However, in the interest of expediting prosecution of this application, Applicants have amended the claims to recite antibodies "which bind to an epitope" which is "also recognized by a monoclonal antibody selected from an E99, a J415, a J533 or a J591 monoclonal antibody." The Examiner has indicated in telephone interviews that such an amendment would obviate this rejection.

For these reasons, Applicants request withdrawal of the rejections under 35 U.S.C. §112, 1st paragraph.

Claim Rejections – 35 U.S.C. §112, 2nd paragraph

The Examiner rejected claims 140-152 as indefinite for reciting "cytotoxic drug" in claims 69, 83, 89, and 128, without sufficient antecedent basis. Claim 140 has been amended to depend from claim 139, thus, Applicants request withdrawal of the rejection.

Claim Rejections – 35 U.S.C. §102

The Examiner has rejected claims 69-71, 77-78, 126-127, 136-137, 139, 140, 141, and 150-158 under 35 U.S.C. 102(e) as allegedly anticipated by Israeli et al. (U.S. Pat. No. 5,538,866). The Examiner relies on Israeli et al. as "in general, teach[ing] antibodies which bind to PSMA and include extensive structural information including the entire nucleic acid sequence of the antigen and the guidance necessary to create antibodies to **any** portion of the antigen." (Office Action, p.8; emphasis in original). However, in order for a reference to anticipate a claim, the reference must teach each and every element of the claim. The claims, as amended, recite antibodies that bind to specific epitopes of PSMA for the treatment and prevention of prostate cancer. Israeli et al. do not teach or suggest antibodies that bind to the specific epitopes recited in the invention.

For these reasons, the present claims are not anticipated by Israeli et al., and the Applicants request withdrawal of the rejection under 35 U.S.C. §102(e).

Claim Rejections – 35 U.S.C. §103

Claims 69-78, 123-127, 136-149, and 159 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Israeli *et al.*(US Patent No. 5,538,866, October, 1994) in view of Thomas *et al.*, (Antibodies, A Practical Approach, V.2 1988) or Schlom (Molecular Foundations of Oncology, Ch. 6, pp.93-94, 1991). As discussed above, Israeli neither teaches nor suggests methods of treating, preventing, or delaying the development or progression of prostate cancer using antibodies or antigen-binding portions thereof that bind to the specified epitopes of PSMA as recited in the present claims. The teachings of Schlom or Thomas et al. have nothing at all to